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Attorney's Docket No.: 16163-005001 / AM100379

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: William Stuart Somers *et al.*	Art Unit	: 1646
Serial No.	: 09/903,876	Examiner	: M. Pak
Filed	: July 11, 2001		
Title	: CRYSTAL STRUCTURE OF ESTROGEN RECEPTOR-BETA COMPLEX AND USES THEREOF		

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P.O. Box 1450
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BRIEF ON APPEAL

Appellants are appealing the final rejection of claims 7-13, 16, and 17 in the Office Action dated February 8, 2005, and the Advisory Action dated July 29, 2005. A Notice of Appeal was filed August 8, 2005, and was received by the U.S. Patent and Trademark Office on August 10, 2005.

(i) Real Party in Interest

The Real Party in Interest is Genetics Institute, LLC, the assignee of record, which is a wholly owned subsidiary of Wyeth.

(ii) Related Appeals and Interferences

There are no pending related appeals or interferences.

(iii) Status of Claims

Claims 1-6, 14 and 15 are canceled.

Claims 7-13, 16, and 17 are rejected and under appeal.

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(iv) Status of Amendments

No amendments are being submitted herewith.

(v) Summary of Claimed Subject Matter

The invention relates to methods for identifying agents, including activators and inhibitors, that interact with Estrogen Receptor-ß (ER-ß). Claims 7 and 9 are the independent claims. **Independent claim 7** is directed to methods for identifying an agent that interacts with ER-ß that include providing a crystal structure of ER-ß that has a resolution of 1.83 Å or less, and generating a three-dimensional model of ER-ß using the relative structural coordinates provided in Figure 2, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Å. The relative structural coordinates provided in Figure 2 are based on the crystal structure of ER-ß. The three-dimensional model is then employed to design or select an agent that interacts with ER-ß. Support for independent claim 7 can be found in the specification, *e.g.,* at page 4, paragraph 9 (lines 14-20); page 11, paragraph 30 (lines 13-19); and page 21, Table 1. **Independent claim 9** is directed to methods for identifying an activator or inhibitor of ER-ß that include providing a crystal structure of ER-ß that has a resolution of 1.83 Å or less, and generating a three-dimensional model of ER-ß using the relative structural coordinates of amino acid residues Met343, Leu346, Leu349, Glu353, Met384, Leu387, Met388, Arg394, Phe404, Ile421, Ile424, Gly520, His523, and Leu524 according to monomer A of Figure 2 or amino acid residues Met343, Leu346, Leu349, Glu353, Met384, Leu387, Met388, Leu391, Arg394, Phe404, Ile421, Ile424, Gly520, His523, and Leu524 according to monomer B of Figure 2. The three-dimensional model is according to the crystal structure coordinates of the amino acids residues of Figure 2, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Å. Computer-fitting analysis of candidate activators or inhibitors with the three-dimensional model is then used to select or design a candidate activator or inhibitor. Support for independent claim 9 can be found in the specification, *e.g.*, at page 4, paragraph 10 (line 21 through page 5, paragraph 10, line 16); page 12, paragraph 32 (lines 21 through page 13, line 9); and page 21, Table 1.

(vi) Grounds of Rejection

Claims 7-13, 16 and 17 are rejected under 35 U.S.C. § 101.

Claims 7-13, 16 and 17 are rejected under 35 U.S.C. § 112, first paragraph for failure to comply with the written description requirement.

Claims 7-13, 16 and 17 are rejected under 35 U.S.C. § 103(a) for being unpatentable over Ljunggren *et al.* (U.S. 6,228,990) in view of Donner *et al.* (U.S. 2003/0167999 A1).

(vii) Argument

I. The subject matter covered by the claims satisfies the utility requirement.

Claims 7-13, 16 and 17 stand rejected for lack of utility because the claims "are drawn to a method of using computer algorithm which is non statutory because claims are drawn to abstract ideas without practical application that is tangible." *See* Office Action mailed February 8, 2005, at page 2. However, the claims cover patentable subject matter because the claims cover *in silico* screening methods that use structural information, and the Trilateral Report issued by the U.S.P.T.O. has determined that such methods are indeed patentable. Appellants previously made this argument, but the Examiner maintained the rejection, stating that the Trilateral Report is not binding. *See* Advisory Action mailed July 29, 2005, at page 2.

A. Appellants' claims are consistent with 3-D Structure-Related Claims determined by the U.S.P.T.O. to satisfy the utility requirement.

In November 2002, the European Patent Office, Japan Patent Office and U.S.P.T.O. jointly released the "Trilateral Project WM4 Comparative Studies in New Technologies: Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims" ("the Trilateral Report"). The purpose of the collaborative report between the three offices was "to enhance mutual understanding concerning the examination of 3-D structure related claims." *See* the Trilateral Report at page 1. Appellants believe that this report indicates the official view of the U.S.P.T.O. regarding the patentability of claims directed to protein 3-D structure related claims, which is the subject of the claimed invention. Appellants also believe that the examining corps is required to follow guidance of the U.S.P.T.O. provided in the Trilateral Report.

In case 6 of the Trilateral Report, claim 1 is directed to an *in silico* screening method using specific known protein P. At pages 10 and 70 of the report, the hypothetical specification of case 6 is described as including an explanation that protein P activity was previously known to lower blood pressure. The hypothetical specification also speculates that by using binding pocket prediction programs and *in silico* screening methods, the person skilled in the art can identify compounds that bind to the protein. The Trilateral Report, at pages 24 and 71, and referring to the claim of case 6, states that

> the utility of the claimed method depends on the utility of the candidate compounds identified as a result of the screening methods. The specification teaches that protein P, when active, lowers blood pressure, however there is no indication whether there is a correlation between binding activity and activation. The claims complies with the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be accepted as a specific, substantial, and credible utility (emphasis added).

Like the hypothetical claim presented in case 6 of the Trilateral Report, Appellants' claims to *in silico* screening methods use a specific known protein (ER-ß). Also like the hypothetical claim presented in case 6, the specification of the pending application discloses that the *in silico* screening methods can be used to identify compounds that bind to the protein. *See* the Specification at pages 4-5, paragraphs 9-10, and pages 11-14, paragraphs 30-32. The specification of the pending application also discloses that the identified compounds may be used as an activator of ER-ß, *e.g.*, to mimic binding of the natural ligand and thereby function as a carcinogen, or to act as an inhibitor of ER-ß, and potentially function as a cancer therapeutic. *See* the Specification at page 14, paragraph 34. The assertion of these uses for an ER-ß binding compound is credible to one skilled in the art and therefore as stated in the Trilateral Report (and as quoted above) the assertion should be accepted as a specific, substantial, and credible utility.

B. Appellants have asserted a utility that is specific, substantial and credible.

The claims satisfy the utility requirements for patentability as outlined in the U.S.P.T.O. Utility Guidelines Training Materials ("Utility Training Materials"), which is used to instruct Examiners on how to interpret and apply the Utility Guidelines to pending claims. The utility requirement is satisfied if either (i) the Applicant has asserted a utility that is specific, substantial and credible, or (ii) the invention has a well-established utility that is specific, substantial and credible. *See* Utility Training Materials at page 9. The subject matter covered by the pending claims at least satisfies the utility requirement under the first test, because Appellants assert that the invention has at least one utility that is specific, substantial and credible. The subject matter covered by the claims therefore satisfies the utility requirements of 35 U.S.C. § 101.

B1. Asserted Specific Utility

The Utility Training Materials (at page 5) define "specific" utility as a "utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention."

Appellants have asserted a specific utility. The specification discloses that the identified agents can be evaluated for their potential to treat "conditions associated with ER-ß such as cancer" (at page 12, paragraph 31, lines 18-20). The specification at page 12, paragraph 31 (lines 15-18) also discloses that the identified agents can be tested to determine whether they can inhibit or activate binding of ER-ß to the phytoestrogen genistein. *See also* page 2, paragraph 4 (line 2) and page 15, paragraph 37 (lines 9-10). As a result, this asserted utility is unquestionably specific.

B2. Asserted Substantial Utility. The Utility Training Materials (at page 6) define "substantial" utility as "a utility that defines a 'real world' use." As discussed above, Appellants have asserted that the claimed methods are for the identification of agents that have substantial utility in the treatment of conditions associated with ER-ß, such as cancer. *See* the Specification at page 12, paragraph 31 (lines 15-18). The treatment of cancer is without question a real world use. Indeed, the Utility Training Materials acknowledge that the "general rule [is] that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See* Utility Training Materials at page 6. Thus, Appellants have asserted a substantial utility for treating a specific disease, *i.e.*, cancer.

B3. Credibility of Asserted Utility. The Utility Training Materials (at page 5) state that a utility is credible if the asserted "utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion."

Appellants' asserted utility in the specification to use the agents identified by the claimed methods for the treatment of cancer is credible. The specification (at page 2, paragraph 5) discloses that the related receptor ER-α binds the agonists estradiol and diethylbestrol (DES), which were well-known carcinogens at the priority filing date of the application (July 12, 2000), and also binds the antagonists raloxifene and tamoxifen, which were well-known cancer therapeutics at the priority filing date. These four compounds are referenced in the specification at page 2, paragraph 5 (lines 11-12). The specification at page 1, paragraph 4 (line 28 through page 2, line 6) also discloses that

> estrogen receptors function as ligand-activated transcriptional factors that have a modular structure consisting of six discrete domains, named A-F...The E domain of ER-α binds ligands such as 17ß-estradiol and...genistein. The E-domains of ER-α and ER-ß are 59% identical in sequence...The natural ligand, 17ß-estradiol, binds both with similar affinity. In contrast, genistein is selective, having 30 fold greater affinity for ER-ß than for ER-α...

Thus ligands (other than 17ß-estradiol and genistein, such as DES, tamoxifen and raloxifene) that bind one estrogen receptor are highly likely to bind the second estrogen receptor to elicit similar although sometimes distinct effects. It is thus reasonable that agents that bind ER-ß, and that are identified by the claimed methods, can be considered candidates for the treatment of cancer. This asserted utility is therefore (A) not seriously flawed, and (B) not inconsistent with the logic underlying the assertion. Accordingly, the asserted utility is credible.

In view of the above arguments, Appellants request reconsideration and withdrawal of the rejection of claims 7-13, 16 and 17 under 35 U.S.C. § 101.

II. The specification adequately describes the claimed subject matter.

Claims 7-13, 16 and 17 stand rejected under 35 U.S.C. § 112, first paragraph, because "the range [of 1.83-1.8 Å] does not provide support for the generic claim limitation '1.83 Å or less,' because it does not provide support for large genus of less than 1.8 Å" (Advisory Action at page 2).

As stated by the United States Court of Appeals for the Federal Circuit, "Although [the applicant] does not have to describe exactly the subject matter claimed,...the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing In re Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989)). Furthermore, "[T]he test for sufficiency of support in a patent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985)).

Appellants believe that the specification satisfies the written description requirement. For example, in Example 1 at pages 15-22, Appellants disclose a crystal structure of ER-ß complexed with genistein. The specification generally discloses that the crystal is a "1.8 Å crystal structure," (page 15, paragraph 37) and more specifically discloses that the crystal structure has a resolution of 1.83-1.8 Å. *See* Table 1 at page 21. In view of this disclosure, one skilled in the art of protein crystallography would understand that Appellants had possession of crystal structures having a resolution of 1.83 Å or less. Appellants therefore request reconsideration and withdrawal of the rejection of claims 7-13, 16 and 17 under 35 U.S.C. § 112, first paragraph.

III. The claims are entitled to domestic priority under 35 U.S.C. § 119(e).

In the final Office Action dated February 8, 2005, the Examiner stated that "the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112 for claims 7-13 and 16-17" (Final Office Action at page 3). The Examiner asserts that the provisional application fails to provide written description support for the pending claims.

Like with the pending utility application, the provisional application discloses a crystal structure that is generally described as a "1.8 Å crystal structure," (page 15, paragraph 37). As with Table 1 in the pending utility application, Table 1 at page 21 of the provisional application discloses that the crystal structure has a resolution of 1.83-1.8 Å. In view of this disclosure, and as discussed above, one skilled in the art of protein crystallography would understand that Appellants had possession of crystal structures having a resolution of 1.83 Å or less at the time of the filing of the provisional application. Appellants therefore believe that their request for domestic priority under 35 U.S.C. § 119(e) should be approved, and ask that the present application be granted the benefit of the filing date of the provisional application, which is July 12, 2000.

IV. The claims are patentable over Ljunggren *et al.* (U.S. 6,228,990) and Donner *et al.* (U.S. 2003/0167999 A1).

In the Final Office Action dated February 8, 2005, the Examiner rejected claims 7-13, 16 and 17 under 35 U.S.C. § 103(a) as being unpatentable over Ljunggren *et al.* (U.S. 6,228,990) in view of Donner *et al.* (U.S. 2003/0167999 A1). However, neither Ljunggren nor Donner, alone or in combination, disclose or suggest the methods covered by the claims, and there is no suggestion to combine the references to provide the methods covered by claims 7-13, 16 and 17. Furthermore, neither Ljunggren nor Donner, alone or in combination, enable the methods covered by these claims. But, as explained by the United States Court of Appeals for the Federal Circuit in Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989): "[i]n order for the prior art to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."

Ljunggren discloses a crystal of ER-β, but the crystal has a resolution of greater than 1.83 Å. Ljunggren provides absolutely no guidance regarding how to make a crystal of ER-β with a resolution of 1.83 Å or less.

Donner does not even disclose a crystal of ER-β. Further, while Donner states that a crystal of human androgen receptor (hAR) "[p]referably has a resolution of from about 1.5 Å to about 3.5 Å" (Donner *et al.*, p. 6, par. 87), the hAR crystal generated by Donner's methods only had a resolution to 2.4 Å. *See*, Donner *et al.*, p. 21, Table 1. Thus, beyond not even disclosing

how to make a crystal of ER-β, Donner does not disclose how to make a crystal of <u>any</u> type with a resolution of 1.83 Å or less.

Appellants therefore request reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 103(a).

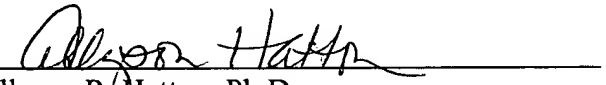
CONCLUSION

For the reasons set forth above, Appellants respectfully request that the rejection of claims 7-13, 16 and 17 be reversed. An appendix containing a copy of the claims under appeal is attached.

Enclosed is a check for $500 for the brief fee and a $120 check for the fee for a Petition for Extension of Time for one month. Please apply any other necessary charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 16163-005001.

Respectfully submitted,

Date: November 2, 2005



Allyson R. Hatton, Ph.D.
Reg. No. 54,154

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

(viii) Claims Appendix

7. A method for identifying an agent that interacts with ER-β, the method comprising:

(a) providing a crystal structure of ER- β having a resolution of 1.83 Å or less;

(b) generating a three dimensional model of ER-β using the relative structural coordinates according to Figure 2, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, the relative structural coordinates being based on the crystal structure of ER-β; and

(c) employing the three-dimensional model to design or select an agent that interacts with ER-β.

8. The method of claim 7, further comprising:

(d) obtaining the agent; and

(e) contacting the agent with ER-β in order to determine the effect the agent has on ER-β activity.

9. A method for identifying an activator or inhibitor of ER-β, the method comprising:

(a) providing a crystal structure of ER-β having a resolution of 1.83 Å or less;

(b) generating a three dimensional model of ER-β using (i) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, ARG394, PHE404, ILE421, ILE424, GLY520, HIS523 and LEU524 according to Figure 2 for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, the relative structural coordinates of the amino acid residues for monomer A of ER-β being based on the crystal structure of ER-β or (ii) the relative structural coordinates of amino acid residues MET343, LEU346, LEU349, GLU353, MET384, LEU387, MET388, LEU391, ARG394, PHE404, ILE421, ILE424, GLY520, HIS523 and LEU524 according to Figure 2 for monomer B of ER-β, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, the relative structural coordinates of the amino acid residues for monomer B of ER-β being based on the crystal structure of ER-β; and

(c) selecting or designing a candidate activator or inhibitor by performing computer fitting analysis of the candidate activator or inhibitor with the three dimensional model generated in step (b).

10. The method of claim 9, wherein the structural coordinates according to (i) further comprise the relative structural coordinates of amino acid residues VAL328, MET342, SER345, THR347, LYS348, LEU349, ALA350, ASP351, LEU354, MET357, TRP383, GLU385, VAL386, MET389, GLY390, LEU391, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, VAL535, TYR536 and LEU538 according to Figure 2 for monomer A of ER-β, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, the relative structural coordinates of the amino acid residues for monomer A of ER-β being based on the crystal structure of ER-β.

11. The method of claim 9, wherein the relative structural coordinates according to (ii) further comprise the relative structural coordinates of amino acid residues MET342, SER345, THR347, LYS348, ALA350, ASP351, MET357, TRP383, GLU385, VAL386, LEU387, MET389, GLY390, MET392, LEU402, ILE403, ALA405, LEU408, VAL418, GLU419, GLY420, LEU422, GLU423, PHE425, LEU428, ALA516, SER517, LYS519, MET521, GLU522, LEU525, ASN526, MET527, LYS528, VAL533, TYR536 and LEU538 according to Figure 2 for monomer B of ER-β , ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, the relative structural coordinates of the amino acid residues for monomer B of ER-β being based on the crystal structure of ER-β.

12. The method of claim 9, further comprising the steps of:

(d) obtaining the candidate activator or inhibitor; and

(e) contacting the candidate activator or inhibitor with the molecule or molecular complex and determining the effect the candidate activator or inhibitor has on the molecule or molecular complex.

13. The method of claim 12, wherein the candidate activator or inhibitor is contacted with the molecule or molecular complex in the presence of genistein to determine the effect the candidate activator or inhibitor has on binding of the molecule or molecular complex to genistein.

16. The method of claim 7, wherein the crystal structure of ER-β has a resolution of 1.8 Å.

17. The method of claim 9, wherein the crystal structure of ER-β has a resolution of 1.8 Å.

(ix) Evidence Appendix

None

(x) Related Proceedings Appendix

None